

## Vitamin D is an Adjuvant Therapy for Egyptian Children with Autism

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### Abstract

**Background:** Many previous publications reported role of vitamin D insufficiency in pathogenesis of many disorders including psychiatric diseases such as autism and its mimic conditions. Few numbers of publications have studied role of vitamin D in development of autism in childhood.

**Aim:** The aim this work was to study the status of vitamin D in autistic children by evaluation of serum levels of 25-hydroxy vitamin D (25 (OH) vitamin D) in Autistic pediatric patients and to study the beneficial role of vitamin D therapy as adjuvant therapy for this disease.

**Materials and methods:** This study was conducted on forty pediatric patients who achieved the diagnostic criteria of autism depending on the 4th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-4). Thirty age and sex matched children served as control group. They were selected from pediatric and neuropsychiatric departments of Tanta Faculty of Medicine. All subjects were subjected to complete history taking, full medical examination, childhood autism rating scale (CARS) assessment and serum 25 (OH) vitamin D assay by enzyme-linked immunosorbent assay (ELIZA).

**Results:** This study reported that 25 (OH) vitamin D levels in children with autism was significantly lower than the controls and it had significant negative correlation with CARS which was improved after vitamin D supplementation at a dose of 400 units daily for eight weeks.

**Conclusion:** Vitamin D is insufficient in most of children with Autism, vitamin D supplementation can improve autistic features in these children.

**Keywords:** Autistic children; Childhood autism rating scale; 25 (OH) vitamin D

### Introduction

25-hydroxy vitamin D (25 OH Vitamin D), the major biochemical form of vitamin D in blood should be measured to evaluate the condition of vitamin D [1]. The fully active form 1,25 dihydroxy vitamin D<sub>3</sub> ((1,25 (OH)<sub>2</sub> vitamin D)) as active form is formed in the renal tissue by the enzyme 25-(OH) vitamin D-1 $\alpha$  hydroxylase. Vitamin D plays a significant role in bone health. A growing evidence based medicine confirmed its important roles in tissues other than bones tissues [1]. Previous researches reported that vitamin D insufficiency or deficiency was involved in pathogenesis of many disorders like psychiatric disorders namely autistic spectrum disorders (ASD) [2,3], cardiac diseases complicating diabetes mellitus and hypertension [4], systemic Lupus erythematosus (SLE), juvenile idiopathic arthritis, Crohn's disease [5], malignancy [6], some respiratory viruses and reactive airway diseases [7] even multiple sclerosis in adults [8]. Authors suspected that in vitamin D deficiency, all endocrinal, autocrinal and paracrine functions of vitamin D disturb leading to variable forms of diseases. Vitamin D as a steroid hormone can maintain calcium hemostasis thus bone metabolism [9]. The 1 $\alpha$ -hydroxylase enzyme is abundant in variable non renal tissues so locally

synthesized active form presents in most of human organs as it is under autonomous autocrine control [10]. Recently it was reported that 1 $\alpha$ -hydroxylase enzyme can activate 25 (OH) vitamin D to active form in the central nervous system [11]. ASD are wide variety of developmental disorders of CNS characterized by disturbed social interaction, impaired speech and stereotypic movements [12]. Deficient serum vitamin D levels have been involved in variable psychological diseases in adulthood such as major psychiatric disorders namely schizophrenia. Little researches have reported on the role of vitamin D in children with ASD like autism and mimic conditions. So the aim of this work was to evaluate the vitamin D status in autistic children by assessment of serum levels of 25 (OH) vitamin D and to evaluate vitamin D as adjuvant therapy for autism.

### Materials and Methods

#### Design of the study and setting

This study was done after approval of ethical research committee of Tanta University Hospital and after an informed oral or written consents of parents of all subjects involved in this study.

We performed this study on 40 children with autism. They were recruited from the psychiatric clinic of pediatric department and

neuropsychiatric department of Tanta University Hospital (TUH) in Egypt. The autism group comprised 27 boys and 13 girls. The ages of them ranged from 4.9 to 11.2 years (mean  $\pm$  SD=9.15  $\pm$  1.17 years). In addition to 30 age and sex matched children as control group. The ages of them ranged from 5 to 15 years (their mean  $\pm$  SD value=8.63  $\pm$  2.65 years).

### Inclusion criteria

Patients achieving criteria of diagnosis of autism as detected by 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [13].

All patients and controls in this study should have equal times of exposure to sun weekly and all of them were from the same Delta Region (Algharbia, Menufia, Dakhalia, Kafer El-Sheik or Albeherah Governates in Egypt).

All patients and controls were studied during summer months (From April 2016 to September 2016) to prevent the effects of seasonal variations serum 25 hydroxy vitamin D levels.

### Study measurements

All children in this study were subjected to detailed history taking from parents of included children includes age, sex, residence, past and family history of different diseases, prior vitamin D or Ca supplementation and sun exposure.

Complete physical examination included anthropometric measures emphasising on weight, height, body mass index (BMI) and full neurological examination. The degree of the severity of autistic features was evaluated by estimation of Childhood Autism Rating Scale (CARS) [14] which classifies the autistic children on a scale from 1 to 4 in each of 15 areas (relating to patients, emotional response, imitation, body use, object use, listening response, fear or nervousness, verbal communication, non-verbal communication, activity level, degree of intellectual function, adaptation to change, visual response, special sense (taste, smell and touch response) and general impressions).

As regard to the CARS scale, patients who have scored from 30 to 36 have mild to moderate degree of autism (n=28) (70%), while patients with from 37 to 60 points have a severe degree of autism (n=12) (30%).

CARS was measured before and after vitamin D supplementations at a dose of 400 unit daily for eight weeks for autistic children.

### Laboratory investigations

- Serum calcium levels.
- Serum 25-(OH) vitamin D levels, which were estimated by enzyme-linked immunosorbent assay (ELISA).

As regard to recent vitamin D recommendations, vitamin D status can be classified into two groups.

1. Vitamin D insufficiency was defined as serum 25-hydroxy vitamin D levels from 25-50 ng/mL.
2. Vitamin D deficiency was defined as serum 25-hydroxy vitamin D levels <25 ng/mL [15].

### Statistical analysis

Data was collected and analyzed using Statistical Package for Social Sciences (SPSS) (version 12). Data was expressed as range and Mean  $\pm$

SD. Statistical tests were unpaired Student's t test, The Mann-Whitney U test, Analysis of variance (F test). The relationship between parameters was assessed using Spearman's correlation test. Statistical significance was defined as p<0.05 [16].

### Results

Variable	Autistic children (n=40)	Control (n=30)	P value
Age			
Range (years)	4.9-11.2	5-15	0.26
Mean $\pm$ SD (years)	9.15 $\pm$ 1.17	8.63 $\pm$ 2.65	
Sex			
Male (No (%))	27 (67.5%)	20 (66.67%)	>0.05
Female (No (%))	13 (32.6%)	10 (33.33%)	
BMI (Mean in kg)	22	21.8	0.72
CARS scale			
$\leq$ 36 (Mild-moderate autism) (No (%))	28 (70%)	-	-
>36 (Severe autism) (No (%))	12 (30%)	-	
Vitamin D status			
Vitamin D deficiency (No (%))	12 (30%)	0 (0%)	<0.05
Vitamin D Insufficiency (No (%))	24 (60%)	0 (0%)	
Normal Vitamin (No (%))	4 (10%)	40 (100%)	

**Table 1:** Demographic data of the studied autistic children and controls.

	Autistic children	Controls	P value
Total Serum Ca level			
Range	6.7-7.2	7.8-11.2	0.032
Mean	6.93	10.2	
SD	$\pm$ 0.23	$\pm$ 0.28	
Serum 25 OH vitamin D (ng/mL)			
Range	18-48	50-75	0.028
Mean	30.4	60.2	
SD	$\pm$ 13.3	$\pm$ 14.1	

**Table 2:** Laboratory investigations of the studied autistic children and controls.

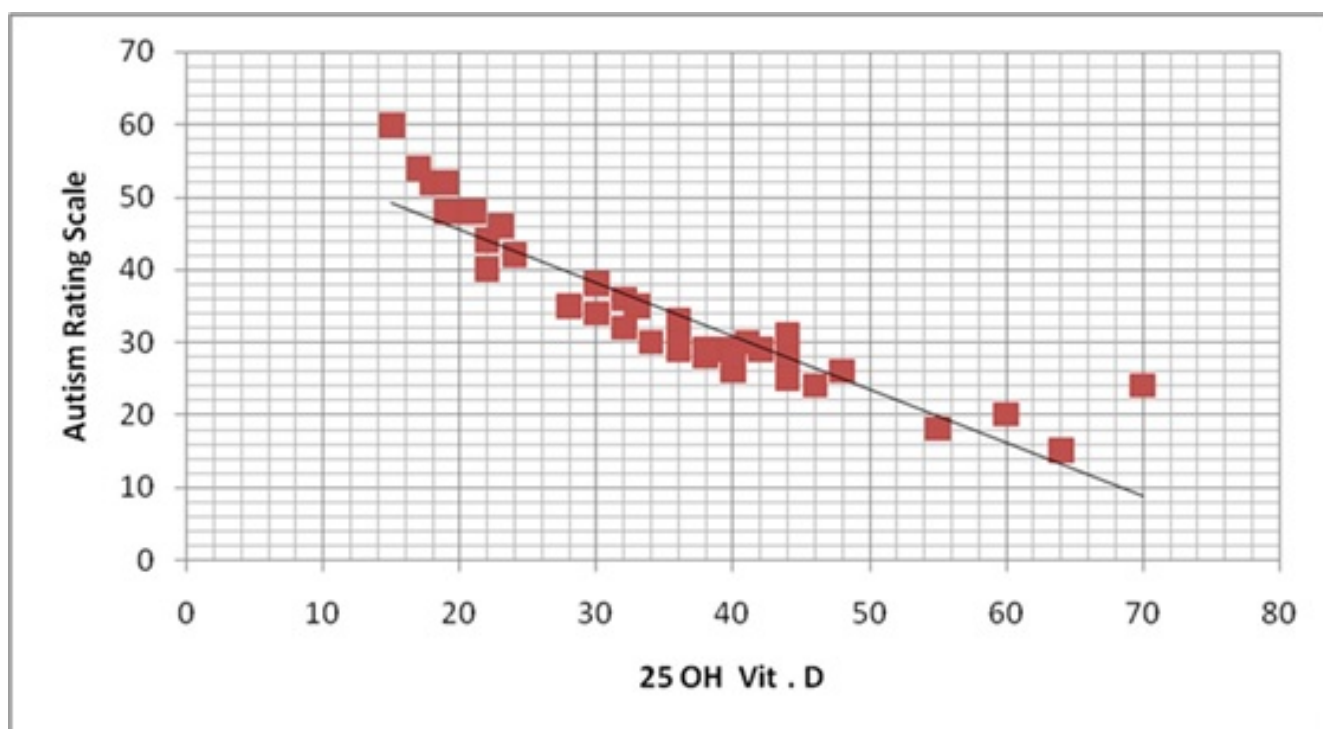
The demographic data of studied groups was represented in Table 1. The studied subjects (patients and controls) had no significant difference in BMI based on age and sex. As regard studied patients, 30% and 60% were being vitamin D deficient and insufficient respectively. The laboratory data of studied groups was represented in Table 2. Serum calcium levels were significantly lower in the patients

than in the controls ( $6.93 \pm 0.23$  mg%, versus  $10.2 \pm 0.28$  mg%) ( $p < 0.05$ ). Mean 25 (OH) D assay in patients with autism was significantly lower than that of the controls ( $30.4 \pm 13.3$  ng/mL, versus  $60.2 \pm 14.1$  ng/mL) ( $p < 0.05$ ). Table 3 reported the mean value of CARS before and after vitamin D supplementation at a dose of 400 units daily for eight weeks for autistic children. There was a marked reduction in the autistic disease activity from severe to mild and also to moderate degrees as evidenced by improvement of CARS after vitamin D supplementation at a dose of 400 unit daily for eight weeks (from 40 to 35) but without statistical significance ( $p > 0.05$ ). Serum 25-OH vitamin D had statistically significant negative correlation with childhood

autism rating scale (CARS) which reflected disease severity ( $P < 0.001$ ) (Figure 1).

Mean of childhood autism rating scale (CARS) in children with autism		
CARS before vitamin D supplementation	CARS after vitamin D supplementation	P value
44	35	>0.05

**Table 3:** Mean childhood autism rating scale (CARS) before and after vitamin D supplementation.



**Figure 1:** Relation between childhood autism rating scale and serum 25-OH vitamin D.

## Discussion

It is proposed that vitamin D deficiency is associated with some psychiatric disorders which have developmental bases, such as major psychiatric disorder namely schizophrenia [17]. Vitamin D deficiency in early infancy affects differentiation of nervous system, connectivity of axons and development of structure and function of CNS [17]. No previous publications about the role of vitamin D deficiency in autistic children. Globally, the prevalence of autism has been rising which attributed to multiple factors such as genetic predisposing namely genetic polymorphisms of cytochrome P450 enzymes specifically CYP27B1 which have been involved in pathogenesis of autism and considered as essential for proper vitamin D metabolism. It is reported that 3 biochemical variants of vitamin D receptors were involved in some psychiatric disorders [17]. No previous studies could clarify role of vitamin D in autism. Serotonin and vitamin D have been suspected to be involved in pathophysiology of autism, but no known mechanism has been reported. Calcitriol (vitamin D hormone) can activates the transcription of the serotonin-synthesizing gene tryptophan hydroxylase 2 (TPH2) in the CNS at a vitamin D response element

(VDRE) and represses the transcription of TPH1 in tissues outside the blood-brain barrier at a distinct VDRE [18].

In the present work, we evaluated serum 25 (OH) vitamin D status in autistic children in comparison to healthy control children. Our results showed that our autistic patients had statistically significant decrease in serum levels of 25-OH vitamin D than healthy controls, with 30% (12 patients) and 60% (24 children) were vitamin D deficient and insufficient, respectively. This is coincident with the findings of Meguid et al. [19] and Mostafa G et al. [20] who reported reduced level of 25 OH Vitamin D in patients with autism when compared to healthy children. Our results showed that there was improvement of mean childhood autistic rating scale (CARS) after vitamin D supplementation of 400 units daily for 8 weeks but not to the degree to be significant and the improvement was more in patients with vitamin D deficient autistic children.

It is proposed that vitamin D theory of pathogenesis of autism cannot decrease the genetic predispositions to development of ASD. Marked vitamin D deficiency in pregnant women or in early infancy can cause marked skeletal abnormalities but cannot precipitate autistic

features in absence of genetic predisposition to autism. Indeed maternal and early infantile vitamin D deficiency may allow the genetic predisposing for ASD to express itself. If this theory will become evidently true, the dream of effective prophylaxis and perhaps a therapy will become so simple, so safe, so inexpensive, so readily available and so easy to achieve.

## Conclusion

Vitamin D deficiency or insufficiency were found in about one third and two thirds respectively in our studied autistic children and vitamin D supplementation at a dose of 400 units daily for eight weeks can improve some autistic features in these children. We concluded that according to our data in this study. There are many possibilities for interpretation of our results, one of them is nutritional deficiency of vitamin D as co morbidity for autism, other possibility is (autism and vitamin D deficiency may be a syndrome). So the observed beneficial effects of vitamin D as adjuvant therapy for improvement of CARS in autistic children may not be necessarily due to autism per se but due to treatment of associated nutritional vitamin D deficiency.

## Recommendations

Vitamin D supplementation can improve autistic features in these children. But, future research works on larger scale for study of suspected potential effects of vitamin D in the pathogenesis and therapy of ASD are warranted.

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